Challenges in Non-Clinical Testing of Hemostatic Medical Devices for Trauma Use

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Various Compositions of Hemostatic Devices

- Animal Tissue (e.g., Collagen, Gelatin, Chitosan, Thrombin)
- Derived from Plants (e.g,. Alginate)
- Mineral-Based (e.g., Kaolin, Zeolite)
- Synthetics (e.g., Polyester, Carboxymethylcellulose)

Issues with Animal Source Material

- Sourcing Issues
  - Animal Husbandry
  - Control of Tissue Collection
  - Manufacturing Controls for Animal Tissue Components
  - Sterilization (and Virus Validation Studies)

Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices) (Draft)

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm381379.htm

Considerations for Non-Clinical Testing

For Potential Battlefield Products

- Consider Environmental Conditions
  - Temperature
  - Altitude
  - Humidity
  - Robustness of Packaging
- Consider the User
  - Labeling revisions based on bench/animal experience

Biocompatibility - Use of ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" – Draft Guidance 2013

- Series of standardized tests
- Dependent on:
  - Time of contact
  - Type of contact
- Works for many, but not all biomaterials

Device Categories			Biological Effect							
Body Contact (see 4.1)		Contact duration (see 4.2) A-limited (24h) B-prolonged (24h to 30 days) C-permanent (>30days)	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	System Toxicity (Acute) Sub-chronic toxicity (sub-acute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface devices	Skin	A	x	x	x	.	.	.	.
		B	x	x	x	.	.	.	.
		C	x	x	x	.	.	.	.
	Mucosal membrane	A	x	x	x	.	.	.	.
		B	x	x	x	o	o	o	.
		C	x	x	x	o	x	o	.
	Breached or compromised surfaces	A	x	x	x	o	.	.	.
		B	x	x	x	o	o	o	.
		C	x	x	x	o	x	o	.
External communicating devices	Blood path, indirect	A	x	x	x	x	.	.	x
		B	x	x	x	x	o	.	x
		C	x	x	o	x	x	o	x
	Tissue/bone/ dentin communicating+	A	x	x	x	o	.	.	.
		B	x	x	o	o	o	x	x
		C	x	x	o	o	o	x	x
	Circulating blood	A	x	x	x	x	.	o^	x
		B	x	x	x	x	o	x	o
		C	x	x	x	x	x	x	o
Implant devices	Tissue/ bone	A	x	x	x	o	.	.	.
		B	x	x	o	o	o	x	x
		C	x	x	o	o	o	x	x
	Blood	A	x	x	x	x	.	.	x
		B	x	x	x	x	o	x	x
		C	x	x	x	x	x	x	x

Biocompatibility - Use of ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" – Draft Guidance 2013

Points of Interest (pp. 9 – 13)

- Final Product or Representative Sample?
- *In Situ* Polymerizing Material
- Bioabsorbable Material
- Biological Response Resulting from Device Mechanical Failure
- Submicron or Nanotechnology Components
- Multiple components or materials in a single sample

Biocompatibility- Use of ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" – Draft Guidance 2013

- Sources of Information
  - In-house studies
  - Master Files from Raw Material Suppliers
  - Published Literature
  - Others? (e.g., MSDS)

Situations where Standard Biocompatibility Tests may be less than optimal

- **Final Product or Representative Sample?**
  - Animal Tissue / Scaffold construct
  - Sealant / Patch – Crosslinked *in situ*
  - Surgical Instrument Models for TSE

"Certain instrument features are particularly difficult to clean – hinges, mated surfaces and lumens. Many TSE investigators are now using small (5 mm) stainless steel wires coated with inoculum in their studies of TSE transmissibility. The material is a suitable stand-in for many instruments."

(page 7 – FDA Briefing Material 9/27/05 – Panel Mtg.

Situations where Standard Biocompatibility Tests may be less than optimal

- *In Situ* Polymerizing and Bioabsorbable Materials
  - Consider the Reagents
  - Consider the Reaction
  - Consider the Final Product
  - Consider the Decomposition Products
  - Kinetics of Resorption

Situations where Standard Biocompatibility Tests may be less than optimal

Submicron or Nanotechnology Components

- Unique properties of submicron / nanotechnology components, (e.g., large surface area / particle, aggregation, agglomeration, immunogenicity, toxicity (altered release kinetics?)
- Rationally designed features that modify host cell response.

Situations where Standard Biocompatibility Tests may be less than optimal

Submicron or Nanotechnology Components

- Consider:
  - Careful characterization of the test sample and extract conditions (e.g., solvent type) to avoid non-clinically relevant testing artifacts
  - Assure that the test article is representative of the clinical product

Resources

Device Search Engines

PMA/510k/MAUDE

http://www.fda.gov/cdrh/databases.html

CDRH - Guidance Database Search Engine

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (Draft)

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf

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